PATENT SPECIFICATION (11) 1 450 030

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(21) Application No. 26679/72 (22) Filed 8 June 1972

(23) Complete Specification filed 10 Sept. 1973

(44) Complete Specification published 22 Sept. 1976

(51) INT. CL.² B01D 13/00

(52) Index at acceptance
B1X 6B4 6B6 6D1 6F4

(19)

(54) PRODUCTION OF SOLUTIONS

(71) We, JAMES GORDON GOW, a British Subject, of Ingerthorpe, 25 Merrilocks Road, Liverpool L23 6UL, Lancashire, and ALAN GORDON ENGLAND, a British Subject, of 18 Cromptons Lane, Liverpool L18 3EX, Lancashire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement.—

The present invention relates to a method of producing aqueous solutions for medical purposes.

Such solutions must be pyrogen free and sterile and must have a low concentration of minerals. It is however inconvenient in many cases for such solutions to be stored at the desired final concentration since this would involve storage of large quantities of liquid much of which is water. It is therefore desirable to store the material or more preferably a concentrated solution thereof and to dilute subsequently. The highly concentrated solutions are made up from sterile pyrogen free water and remain bacteria-free due to their high concentration. Whilst the invention is especially applicable to production of solutions for immediate use, it may also be used to produce solutions which may be stored ready for use.

According to one aspect of the present invention there is provided a method for the production of an aqueous solution of desired concentration for medical purposes which comprises passing water through a reverse osmosis column capable of retaining 100 per cent of pyrogenic materials, and subsequently, in either order, passing the water through a sterilising device capable of eliminating 100 percent of bacterial material, and mixing the water with a material to be dissolved.

Preferably the water is mixed with a solution of the material of higher concentration than desired.

According to another aspect of the present invention there is provided an apparatus for the production of an aqueous solution of desired concentration for medical purposes, which comprises a reverse osmosis column capable of retaining 100 per cent of pyrogenic material, the outlet from which is connected, in either order, to the inlet of a steriliser capable of eliminating 100 percent of bacterial material, and to a proportioning system.

The sterilising device may be of any convenient type. One preferred form of steriliser is a heat steriliser preferably a flash steriliser. In the flash steriliser preferably the temperature of the fluid is raised rapidly to 150 - 160°C for about 1 minute and then cooled to about 40°C.

Another preferred form of steriliser is a filter capable of retaining 100% of bacterial material.

The water and the concentrated solution may be admixed upstream or downstream of the steriliser and the proportioning system may therefore be connected between the outlet from the reverse osmosis column and the inlet to the steriliser or alternatively to the outlet from the steriliser. The former of these two alternatives is preferred.

In this preferred embodiment pryogen free water from the reverse osmosis column is delivered to the proportioning system e.g. a proportioning pump and a pyrogen free, mineral free, sterile, concentrated solution of the material required (e.g. glucose or

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SPECIFICATION NO 1450030

Inventors: JAMES GORDON GOW
ALAN GORDON ENGLAND

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of INGERTHORPE HOLDINGS LIMITED, a British Company, of 26 North John Street, Liverpool L2 9RX

THE PATENT OFFICE

Bas 32445/5

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Such solutions must be pyrogen free and sterile and must have a low concentration of minerals. It is however inconvenient in many cases for such solutions to be stored at the desired final concentration since this would involve storage of large quantities of liquid much of which is water. It is therefore desirable to store the material or more preferably a concentrated solution thereof and to dilute subsequently. The highly concentrated solutions are made up from sterile pyrogen free water and remain bacteria-free due to their high concentration. Whilst the invention is especially applicable to production of solutions for immediate use, it may also be used to produce solutions which may be stored ready for use.

According to one aspect of the present invention there is provided a method for the production of an aqueous solution of desired concentration for medical purposes which comprises passing water through a reverse osmosis column capable of retaining 100 per cent of pyrogenic materials, and subsequently, in either order, passing the water through a steriliser capable of eliminating 100 per cent of bacterial material, and admixing, in suitable ratio, the water with a desired material, or with a solution of such material of higher concentration than desired.

Preferably the water is mixed with a solution of the material of higher concentration than desired.

According to another aspect of the present invention there is provided an apparatus for the production of an aqueous solution of desired concentration for medical purposes, which comprises a reverse osmosis column capable of retaining 100 per cent of pyrogenic material, the outlet from which is connected, in either order, to the inlet of a steriliser capable of eliminating 100 percent of bacterial material, and to a proportioning system.

The sterilising device may be of any convenient type. One preferred form of steriliser is a heat steriliser preferably a flash steriliser. In the flash steriliser preferably the temperature of the fluid is raised rapidly to 150 - 160°C for about 1 minute and then cooled to about 40°C.

Another preferred form of steriliser is a filter capable of retaining 100% of bacterial material.

The water and the concentrated solution may be admixed upstream or downstream of the steriliser and the proportioning system may therefore be connected between the outlet from the reverse osmosis column and the inlet to the steriliser or alternatively to the outlet from the steriliser. The former of these two alternatives is preferred.

In this preferred embodiment pryogen free water from the reverse osmosis column is delivered to the proportioning system e.g. a proportioning pump and a pyrogen free, mineral free, sterile, concentrated solution of the material required (e.g. glucose or glycine) is separately delivered to the proportioning system, which then delivers solution at the required concentration to the steriliser. One proportioning pump which has been found to be suitable has a delivery rate of up to 1½ litres per minute. The proportioning system may operate in various

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ways e.g. measured quantities of water and a solution of known concentration may be admixed (as in a proportioning pump) or the concentration of the diluted solution may be constantly measured and the ratio of water to concentrated solution adjusted to give the correctly diluted solution. This latter method is especially useful when the solution is conductive since the conductivity provides a ready measure of concentration.

In osmosis, flow through the semi-permeable membrane is from the less concentrated phase to the more concentrated phase. By applying sufficient pressure on the more concentrated phase this flow may be reversed thereby causing reverse osmosis to occur.

The reverse osmosis column used in the present invention preferably employs a semi-permeable membrane made from a cellulose base material e.g. cellulose acetate. The membrane may be in many different configurations. It has been found however that a plurality of tubes of the membrane in parallel relationship or one or more spirally wound tubes of the membrane are especially suitable.

Suitable reverse osmosis columns are produced by Millipore (UK.) Limited; Ajax International Corporation; Osmanics Inc. and De Danske Sukkerfabricker A.G. (Membrane type 975 sold by Millipore (UK.) Limited being especially suitable).

Pyrogens are toxic, non dialysable fever producing substances formed by various microorganisms and their exact constitution is at present not known. (The presence of pryogens in a particular solution is detected by a test involving injecting a sample into a rabbit). Pyrogens are believed however to have molecular weight above 2,000. The reverse osmosis column therefore will probably remove all pyrogens if it has a semi-permeable membrane which prevents passage of materials having a molecular weight of 2,000. It is however preferred that the semi-permeable membrane will prevent passage of all materials with a molecular weight above 1,000, more preferably all materials with a molecular weight of 200 and above. Membrane type 975 mentioned above is capable of preventing passage of materials having a molecular weight of 200 and above.

The bacterial filter may be of any type which will retain 100% bacteria. It is however preferred that a surface filter with a specific pore size be used although depth filters which rely on statistic possibilities may also be used.

Preferred surface filters involve the use of a membrane and preferably have a pore size of about 0.2μ. The membranes found to be most useful are composed of pure and biologically inert cellulose esters. Suitable filters are marketed by Millipore (U.K.) Limited under the trade mark MF. Millipore, MF type GS having a pore size of 0.22μ being especially useful (Millipore is a registered Trade Mark).

The bacterial filter may be of the disposable type or may be reusable after cleansing.

It is preferable to pass the water through a pre-filter prior to entering the reverse osmosis column and the pre-filter preferably has a pore size between 0.5 and 10 microns, preferably between 0.5 and one micron. This pre-filter is included to protect the reverse osmosis column and is usually a mechanical filter, preferably made of fibreglass and merely removes relatively large particles.

A pump may be required to maintain an adequate flow rate although in many cases no such pump will be necessary. This applies particularly where the supply of water is taken directly from the mains, since in the majority of cases the mains pressure will be sufficient to maintain an adequate flow rate.

It is preferred that additional safety devices be incorporated. For example a pressure head safety device may be incorporated to ensure correct pressure and/or a bubble test device may be included to check the integrity of the bacterial filter. This latter device is not normally used where a disposable bacterial filter is used. Another safety device which is preferably incorporated is a filter between the outlet from the reverse osmosis column and the inlet to the steriliser together with means for measuring the pressure differential between the two sides of the filter. Thus if the reverse osmosis column fails this additional filter will begin to block and the pressure differential between the two sides of the filter will alter considerably. Preferably the apparatus includes an arrangement whereby any alteration in the pressure differential from its normal range causes the apparatus to be switched off. The filter is preferably a surface type filter and a suitable pore size is of the order of 0.2μ. Where the steriliser is a bacterial filter it is possible though not preferable to avoid the use of an additional filter for this safety device by including means for measuring pressure differential between the two sides of the bacterial filter.

Aqueous solutions from the device of the invention may be used directly or may be stored for subsequent use. If the solution is to be stored it should be subjected to an autoclaving treatment e.g. by steam autoclaving as soon as possible after entering the storage container e.g. the package.

The process of the invention is applicable to production of solutions of for example

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glucose and glycine.

The aqueous solutions produced in accordance with the invention may be used for various medical purposes, e.g. peritoneal dialysis, bladder irrigation and intravenous use. For bladder irrigation the flow rate through the apparatus of the invention is preferably of the order of 2 litres per minute and for peritoneal dialysis a flow rate of the order of ½ litre per minute is desirable.

WHAT WE CLAIM IS:—

1. A process for the production of an aqueous solution of desired concentration for medical purposes which comprises passing water through a reverse osmosis column capable of retaining 100 per cent of pyrogenic materials, and subsequently, in either order, passing the water through a steriliser capable of eliminating 100 per cent of bacterial material, and admixing, in suitable ratio, the water with a desired material, or with a solution of such material of higher concentration than desired.

2. A process as claimed in claim 1, in which the water and the concentrated solution are admixed upstream of the steriliser.

3. A process as claimed in claim 1 or 2, in which the aqueous solution being produced is a solution of glucose or glycine.

4. A process as claimed in any one of claims 1 to 3 in which the water is passed through a pre-filter prior to entering the reverse osmosis column.

5. A process as claimed in any of the preceding claims, in which the aqueous solution produced is subjected to an autoclaving treatment.

6. A process as claimed in any one of claims 1 to 5 in which the steriliser is a filter capable of retaining 100 percent of bacterial material.

7. A process as claimed in claim 6 in which the water is admixed with a solution of higher concentration than desired.

8. A process as claimed in any one of claims 1 to 5, in which the steriliser is a heat steriliser.

9. A process as claimed in claim 8, in which the steriliser is a flash steriliser.

10. A process as claimed in claim 9, in which the water is heated rapidly in the steriliser to 150-160°C for about 1 minute and is then cooled to about 40°C.

11. An apparatus for the production of an aqueous solution of desired concentration for medical purposes, which comprises a reverse osmosis column capable of retaining 100 per cent of pyrogenic material, the outlet from which is connected, in either order, to the inlet of a steriliser capable of eliminating 100 per cent of bacterial material, and to a proportioning system.

12. An apparatus as claimed in claim 11, in which the proportioning system is connected between the outlet from the reverse osmosis column and the inlet to the steriliser.

13. An apparatus as claimed in claim 11 or 12, in which the porportioning system comprises a proportioning pump.

14. An apparatus as claimed in claim 13 in which the proportioning pump has a delivery rate of up to 1½ litres per minute.

15. An apparatus as claimed in any of claims 11 to 14 in which the semi-permeable membrane is made from a cellulose base material.

16. An apparatus as claimed in claim 15 in which the membrane is in the form of one or more spirally wound tubes of the membrane or a plurality of tubes in parallel relationship.

17. An apparatus as claimed in any one of claims 11 to 16 in which the reverse osmosis column has a semi-permeable membrane which prevents passage of materials having a molecular weight of 2,000 and above.

18. An apparatus as claimed in claim 17 in which the semi-permeable membrane will prevent passage of all materials with a molecular weight above 1,000.

19. An apparatus as claimed in claim 18 in which the semi-permeable membrane will prevent passage of all materials with a molecular weight of 200 and above.

20. An apparatus as claimed in any one of claims 11 to 19 in which a pre-filter is located upstream of the reverse osmosis column.

21. An apparatus as claimed in claim 20, in which the pre-filter has a pore size between 0.5 and 10 microns.

22. An apparatus as claimed in claim 21, in which the pre-filter has a pore size between 0.5 and one micron.

23. An apparatus as claimed in any one of claims 11 to 22 which also comprises a pump.

24. An apparatus as claimed in any one of claims 11 to 23, which also comprises a pressure head safety device to ensure correct pressure.

25. An apparatus as claimed in any one of claims 11 to 24, which also comprises a bubble test device to check the integrity of the steriliser.

26. An apparatus as claimed in any one of claims 11 to 19, in which the steriliser is a filter capable of removing 100% of bacterial material.

27. An apparatus as claimed in claim 26, in which the bacterial filter is a surface filter.

28. An apparatus as claimed in claim 27 in which the surface filter has a membrane with a pore size of about 0.2μ.

29. An apparatus as claimed in claim 27 or 28 in which the surface filter has a mem-

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brane composed of pure and biologically inert cellulose ester.

30. An apparatus as claimed in any one of claims 11 to 25, in which the steriliser is a heat steriliser.

31. An apparatus as claimed in claim 30, in which the steriliser is a flash steriliser.

32. An apparatus as claimed in any one of claims 11 to 31, which also incorporates an additional filter between the outlet from the reverse osmosis column and the inlet to the steriliser and means for measuring the pressure differential between the two sides of the filter.

33. An apparatus as claimed in claim 32, in which the additional filter is a surface filter.

34. An apparatus as claimed in claim 32 or 33 in which the additional filter has a pore size of about 0.2μ.

35. An apparatus as claimed in any one of claims 32 to 34, which also includes a device for switching off the apparatus in the event that during operation the pressure differential between the two sides of the additional filter varies from its normal range.

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Chartered Patent Agents.

Printed for Her Majesty's Stationery Office by The Tweeddale Press Ltd., Berwick-upon-Tweed, 1976.
Published at the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

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